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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/429,832      | 10/29/1999  | RAMESH A. BHAT       | 0646/1D205-U        | 6371             |

32801 7590 06/30/2004

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| EXAMINER |
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BASI, NIRMAL SINGH

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| ART UNIT | PAPER NUMBER |
|----------|--------------|

1646

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/429,832

**Applicant(s)**

BHAT ET AL.

**Examiner**

Nirmal S. Basi

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 17, 19-22, 28-30, 34, 35, 38 and 39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 17, 19-22, 28-30, 34, 35, 38 and 39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_.

### DETAILED ACTION

1. Amendment filed 4/5/04 has been entered.
2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 17, 28, 30, 34, 35, 38, and 39 rejected under 35 U.S.C. 102(e) as being anticipated by Mosselman et al (US Patent 6,680,368).

Mosselman discloses an isolated estrogen receptor- $\beta$  (SEQ ID NO: 25) which has 100% query match and 100% best local similarity to the claimed estrogen receptor- $\beta$  of SEQ ID NO: 2. Mosselman further discloses the estrogen receptor- $\beta$  binds 17- $\beta$  estradiol (Figure 2). Mosselman also discloses the estrogen receptor- $\beta$  (SEQ ID NO: 25) can be modified with a label capable of providing a detectable signal (use of firefly luciferase and other detectable labels is disclosed in column 7). Claim 28 requires the

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polypeptide of claim 17 to be modified with a detectable label. Claim 28 requires the polypeptide of claim 17 to be modified with a detectable label that is a fluorescent compound. The limitations of claims 17, 28, 30, 34, 35, 38, and 39 (estrogen receptor- $\beta$  (SEQ ID NO: 2) and estrogen receptor- $\beta$  (SEQ ID NO: 2) modified with a label capable of providing a detectable signal where the label is a fluorescent compound) are met by the disclosure of Mosselman, absent evidence to the contrary.

### ***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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i) Claims 28 and 30 rejected under 35 U.S.C. 103(a) as being unpatentable over Mosselman et al US Patent 6,680,368 in view of The Government of The United States of America (WO 97/20931).

Mosselman discloses an isolated estrogen receptor- $\beta$  (SEQ ID NO: 25) which has 100% query match and 100% best local similarity to the estrogen receptor- $\beta$  of SEQ ID NO: 2 of instant application. Mosselman further discloses the estrogen receptor- $\beta$  binds 17- $\beta$  estradiol (Figure 2). Mosselman also discloses the production of chimeric estrogen receptor- $\beta$ , which would be useful for the identification of ligands, for example (column 6 and 7). Mosselman does not teach an estrogen receptor- $\beta$  of SEQ ID NO: 25 modified with a label that is a green fluorescent protein.

The Government of The United States of America (WO 97/20931) discloses the production of chimeric proteins wherein the fluorescent protein (green fluorescent protein, GFP) can be fused to steroid receptors (glucocorticoid receptor, estrogen receptor etc.), see page 18-19, 23. The chimeric proteins are disclosed to be useful in observing and monitoring the targeting and translocation of steroid receptors in living cells. Further, the chimeric proteins are disclosed to be useful in screening for ligands that bind to or activate steroid receptors, pages 5-7.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use GFP disclosed by The Government of The United States of America to modify the estrogen receptor- $\beta$  of SEQ ID NO: 25 disclosed by Mosselman to produce a chimeric polypeptide containing a label capable of providing a detectable signal. The ordinary artisan would have been motivated to produce the

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fluorescent estrogen receptor- $\beta$  for use in monitoring the targeting and translocation of estrogen receptor- $\beta$  of SEQ ID NO: 25 in living cells and to screen for ligands that bind to or activate said receptor. The ordinary artisan would have expected success at producing an estrogen receptor- $\beta$  of SEQ ID NO: 25, modified with a GFP, because the use of GFP in the production of fluorescent steroid receptors is well known in the art to study protein translocation in a cell. Therefore, the claimed invention was obvious at the time of the invention.

ii) Claims 28-30 rejected under 35 U.S.C. 103(a) as being unpatentable over Mosselman et al US Patent 6,680,368 in view of Buchsbaum et al (US Patent 5,902,583), and further in view of Hochberg (US Patent 4,465,676) and Chang et al (US Patent 6,140,119).

Mosselman discloses an isolated estrogen receptor- $\beta$  (SEQ ID NO: 25) which has 100% query match and 100% best local similarity to the estrogen receptor- $\beta$  of SEQ ID NO: 2 of instant application. Mosselman further discloses the estrogen receptor- $\beta$  binds 17- $\beta$  estradiol (Figure 2). Mosselman also discloses the production of chimeric estrogen receptor- $\beta$ , which would be useful for the identification of ligands, for example (column 6 and 7). Mosselman does not teach an estrogen receptor- $\beta$  of SEQ ID NO: 25 modified with a label that is a radioisotope. Mosselman also does not teach an estrogen receptor- $\beta$  of SEQ ID NO: 2 modified with a label that is a fluorescent antibody or  $^{125}\text{I}$  labeled antibody.

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Buchsbaum discloses the production of radiolabeled antibodies ( $^{125}\text{I}$  labeled) that target specific molecules (Fig 5, for example). Buchsbaum also discloses the production of radiolabeled ligands (tamoxifen, estradiol, estradiol derivatives, estrogen and fluoralanine), which specifically bind to the estrogen receptor (column 7, second paragraph). Buchsbaum further discloses proteins can be easily radioiodinated (column 8, third paragraph). Buchsbaum does not disclose the isolated estrogen receptor- $\beta$  of SEQ ID NO: 25 (Mosselman)

Hochberg discloses radiolabeled estrogens, their radiolabeled analogs (see Examples). Hochberg also discloses the radiolabeled estrogens are useful in estrogen receptor assays, radioimmuno assays, *in vivo* imaging of tissues having estrogen receptor activity (Abstract). Experimental details from kinetic experiments and Scatchard analysis of iodinated estrogen binding to estrogen receptors are disclosed in column 3 and column 5. Hochberg also discloses radiolabeled estradiol can be used to label and detect estrogen receptor on glycerol gradients. Hochberg does not disclose the isolated estrogen receptor- $\beta$  (SEQ ID NO: 25, Mosselman)

Chang discloses the production of immunofluorescent anti-estrogen receptor antibodies and their use in "immune fluorescence staining of estrogen receptor", (column 5). Chang further discloses the use of immunofluorescent anti-estrogen receptor antibodies in the binding to estrogen receptor and their use in Western Blot analysis (column 6). Chang does not disclose the isolated estrogen receptor- $\beta$  of SEQ ID NO: 25 (Mosselman)

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use radiolabeled ligands for the estrogen receptor disclosed by Buchsbaum or Hochberg and use them in the isolation or analysis of the estrogen receptor- $\beta$  disclosed by Mosselman. The binding of a radiolabeled estrogen, an iodinated analog of estrogen or an iodinated derivative thereof to the estrogen receptor- $\beta$  disclosed by Mosselman would inherently create a polypeptide modified with a label capable of providing a detectable signal. Alternatively, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to produce radiolabeled or fluorescent labeled antibodies (Buchbaum and Chang) that specifically bind the estrogen receptor- $\beta$  disclosed by Mosselman and use them in the isolation or analysis of said estrogen receptor- $\beta$ . The binding of a radiolabeled antibody to the estrogen receptor- $\beta$  disclosed by Mosselman would inherently create a polypeptide modified with a label capable of providing a detectable signal. Further, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the iodination technique disclosed by Buchbaum to iodinate the estrogen receptor- $\beta$  disclosed by Mosselman for use in the isolation or analysis of said estrogen receptor- $\beta$ . The iodinated estrogen receptor- $\beta$ , disclosed by Mosselman, would inherently be a polypeptide modified with a label capable of providing a detectable signal. The ordinary artisan would have been motivated to produce the estrogen receptor- $\beta$  modified with a label capable of providing a detectable signal for use in isolation or analysis of the estrogen receptor- $\beta$  e.g. Scatchard analysis, determine ligand binding, isolation on gradients, determine decay rates, targeting and



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translocation analysis, The ordinary artisan would have expected success at producing an estrogen receptor- $\beta$  of SEQ ID NO: 25 modified with a label that is either a radioisotope or has fluorescent properties, because methods for the production of said labels is well known and routine in the art. Therefore, the claimed invention was obvious at the time of the invention.

iii) Claims 19-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Mosselman et al US Patent 6,680,368 in view of Hochberg (US Patent 4,465,676) and further in view of Buchsbaum et al (US Patent 5,902,583),

Mosselman discloses an isolated estrogen receptor- $\beta$  (SEQ ID NO: 25) which has 100% query match and 100% best local similarity to the estrogen receptor- $\beta$  of SEQ ID NO: 2 of instant application. Mosselman further discloses the estrogen receptor- $\beta$  binds 17- $\beta$  estradiol (Figure 2). Mosselman also discloses the production of chimeric estrogen receptor- $\beta$ , which would be useful for the identification of ligands, for example (column 6 and 7). In addition, Mosselman teaches estrogen receptor- $\beta$  of SEQ ID NO: 25 can be used identify functional ligands (agonists and antagonists) for the steroid receptor. Mosselman does not teach the use of labeled ligands in a method for identifying estrogen receptor- $\beta$ -interactive compounds.

Hochberg teaches the use of labeled ligands in a method for identifying estrogen receptor-interactive compounds. Hochberg discloses radiolabeled estrogens, their radiolabeled analogs (see Examples). Hochberg also discloses the radiolabeled estrogens are useful in estrogen receptor assays, radioimmuno assays, *in vivo* imaging of tissues having estrogen receptor activity (Abstract). Experimental details from kinetic

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experiments and Scatchard analysis of iodinated estrogen binding to estrogen receptors are disclosed in column 3 and column 5. Hochberg also discloses an estrogen receptor specificity assay where a series of compounds were allowed to compete with radiolabeled estrogen receptor ligand (labeled estradiol) for sites on the estrogen receptor. The bound and free steroids (ligands) were separated using dextran coated charcoal. It was determined that only compounds with estrogenic activity were active in displacing labeled ligand. The method inherently identified estrogen receptor interactive compounds (Example 9). Therefore, Hochberg discloses contacting an estrogen receptor with a labeled ligand in the presence of test compounds, achieving equilibrium binding of said labeled ligand to said estrogen receptor and determining the level of binding of said labeled ligand to the estrogen receptor, thereby identifying ligands which are agonists or antagonists of said estrogen receptor. Hochberg does not teach estrogen receptor- $\beta$  of SEQ ID NO: 25 (Mosselman)

Buchsbaum discloses the production of radiolabeled antibodies ( $^{125}\text{I}$  labeled) to target specific molecules (Fig 5, for example). Buchsbaum also discloses the production of radiolabeled ligands (tamoxifen, estradiol, estradiol derivatives, estrogen and fluoralanine), which specifically bind to the estrogen receptor (column 7, second paragraph). Buchsbaum further discloses proteins can be easily radioiodinated (column 8, third paragraph). Hochberg does not teach estrogen receptor- $\beta$  of SEQ ID NO: 25 (Mosselman).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to incorporate the estrogen receptor- $\beta$ , disclosed by

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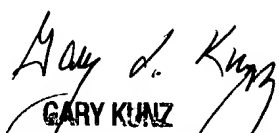
Mosselman, into the method of measuring estrogen receptor ligand specificity, disclosed by Hochberg (Example 9), using the radiolabeled ligands for the estrogen receptor, disclosed by Buchsbaum or Hochberg, because said method would identify estrogen receptor-interactive compounds. The ordinary artisan would have been motivated to use estrogen receptor- $\beta$  disclosed by Mosselman in the method disclosed by Hochberg to isolate ligands that specifically interact with the estrogen receptor- $\beta$  because the isolation of said ligands would be useful in diagnostic purposes, including, applications in estrogen receptor assays, radioassays of estrogens and *in-vivo* imaging of certain organs (see Hochberg, column 1). Further, Mosselman teaches estrogen receptor- $\beta$  of SEQ ID NO: 25 can be used to identify functional ligands (agonists and antagonists) for the said receptor. The ordinary artisan would have expected success in identifying estrogen receptor (SEQ ID NO: 25 disclosed by Mosselman) interactive compounds using labeled ligands, in the method disclosed above, because said method is well known in the art generally applicable to all estrogen receptors. The method of Hochberg is routinely used in the art to identify ligands of steroid receptors. The art provides ample support for the production of labeled compounds that may be used in the method to identify estrogen receptor interactive compounds. Therefore, the claimed invention was obvious at the time of the invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi  
June 23, 2004

  
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